2. SCIENTIFIC ABSTRACT

Degenerative arthritis is the most frequently encountered orthopedic disease associated with cartilage damage and impacts one in seven people. The pathogenesis of degenerative arthritis is the degeneration of the hyaline articular cartilage that becomes deformed, fibrillated, and eventually excavated during the course of the disease. Most methods for treating degenerative arthritis focus on the reduction of the symptomatic pain. If the degenerated cartilage could be regenerated, most patients would be able to function without debilitating pain. Treatment using autologous human chondrocytes to replace damaged cartilage entails two operations with an excision of the soft tissues and requires a lengthy recovery time. Further, these autologous chondrocytes have a limited capacity to regenerate hyaline cartilage.

One of the most important factors in the production of type II collagen by cartilage cells is the presence of transforming growth factor-β1 (TGF-β1). TGF-β is a multifunctional cytokine, playing a regulatory role in cell growth, differentiation, and extracellular matrix protein synthesis and has been reported to induce osteogenesis and chondrogenesis. Studies have also suggested that TGF-β stimulates chondrocyte proteoglycan synthesis and the growth of articular chondrocyte cells. In addition to its stimulatory action on chondrocytes, TGF-β has been shown to possess anti-inflammatory and immune suppressive properties. However, widespread clinical applications of this protein have been limited due to its short-term effects as a result of a short half-life.

TissueGene-C represents a cell-mediated cytokine gene therapy approach for cartilage regeneration. TissueGene-C is a 3:1 mixture of non-transduced allogeneic human chondrocytes (hChon) and allogeneic human chondrocytes transfected with a retroviral vector encoding TGF-β1 (hChonβ1). Cellular production of TGF-β1 can provide longer-term effects of TGF-β1 in stimulating hyaline cartilage generation from only a single product injection without requiring an operation or a lengthy rehabilitation time. The non-transduced chondrocytes are included as additional cells for filling the defect site and as target cells for TGF-β1 expressed from transduced cells because TGF-β1 has both autocrine and paracrine modes of action. TissueGene-C has been shown to successfully form cartilage following s.c. injection in nude mice, whereas no cartilage was formed when the mice were injected with non-transduced chondrocytes. When injected into the damaged knee joints of rabbits and dogs, transduced human chondrocytes have exhibited sustained TGF-β1 release and proliferation of regenerative cartilage with no overgrowth.

The proposed Phase 1 clinical trial is designed to provide safety and preliminary activity data of TissueGene-C in patients with degenerative knee joint disease who are schedule to undergo complete knee replacement. The design is a placebo-controlled, randomized dose-escalation study. In addition to obtaining safety information regarding the injection of TissueGene-C in these patients, this approach will allow us to obtain data regarding the dose-response of the hChonβ1 cells in engrafting at the defect, as well as information regarding any distribution of the hChonβ1 cells out of the injected site. At the time of total knee replacement, resected tissue will be evaluated microscopically for engraftment and subsequent cartilage production, and the joint analyzed for evidence of overgrowth or transformation of the engrafted TissueGene-C product.